

Serial No: 10/024,130
Filed: 12/17/2001
Page 7 of 11

REMARKS

Status of the Claims

Claims 2, 5, 16, 20 and 31 have been amended without prejudice to or disclaimer of the subject matter therein as described elsewhere. Support for these amendments is found in the specification. See page 27, line 3 and the paragraph spanning pages 27-28 of the specification. Therefore, no new matter has been added by amendment. Claims 2-3, 5-16, 20-29 and 31-39 are now pending.

The Examiner's comments in the Final Office Action are addressed below in the order set forth therein.

The Rejections of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 2, 3, 5-16, 20-29, and 31-39 stand rejected under 35 U.S.C. § 103 over Robinson (U.S. Pat. No. 5,589,372) in view of Wolf *et al* (1991) *Analytical Bioch.* 192:78-981, Nakashima *et al.* (1992) *Proc. Nat'l Acad. Sci.* 92:2328-2332, and Ciosek *et al.* (1993) *J. Biol. Chem.* 268:24832-24837. This rejection is respectfully traversed.

Applicants claim methods comprising the determination of squalene synthase activity by combining FPP, NADPH, squalene synthase and a magnesium ion cofactor to form a reaction mixture. The concentration of NADPH over time is determined by subjecting the reaction mixture to UV light and detecting fluorescent light emission. The present rejection fails to carry the Office's burden of demonstrating a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness (1) there must be some suggestion in the reference or knowledge generally available to one of ordinary skill in the art to modify the reference or combine the references; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP § 2143. See *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)(teaching or suggestion to make and reasonable expectation of success must be found in prior art); *In re Royka*, 49 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974)(all limitations must be taught). The Office Action has not met these standards.

Serial No: 10/024,130
Filed: 12/17/2001
Page 8 of 11

The Office Action states that the Robinson reference "provides motivation to one of ordinary skill in the art to develop an easy assay method amenable to automation to use in a method for screening potential inhibitor[s]" of squalene synthase activity. This reasoning is founded on Robinson's discussion of the benefits of reducing squalene synthase activity in tobacco or rubber plants. Contrary to the reasoning of the Office Action, where Robinson discusses the benefits of reducing squalene synthase activity in tobacco or rubber plants, the discussion focuses upon organisms genetically engineered to possess reduced levels of squalene synthase activity. Indeed, the Office Action notes this deficiency by conceding that the "Robinson teaching is directed to a genetically engineered cell." Thus, the portion of the reference referred to in the rejection is irrelevant to screening for inhibitors of squalene synthase inhibitors and would fail to motivate one of skill in the art to develop an assay for inhibitors of the squalene synthase of tobacco or rubber plants (or any plant, for that matter).

Where Robinson does discuss screening for squalene synthase inhibitors, the disclosure specifically teaches assaying for squalene synthase by gas chromatographic quantification of squalene and/or radioassay. See column 8, lines 15-20, citing Biller, S. A. et al., J. Med. Chem. 31, 1869 (1988) (gas chromatography) and EXAMPLE 8, Cloning and Characterization of Human and Schizosaccharomyces pombe Squalene Synthetase cDNAs, I. Materials and Methods, K. Microsomal extracts and squalene synthetase activity, citing Poulter, C. D. and Rilling, H. C. (1981) in Biosynthesis of Isoprenoid Compounds, Porter, J. W., and Spurgeon, S. L., eds., pp. 413-442, Willey, New York (radioassay). Further, Robinson's assays contemplate comparing a host cell with active squalene synthetase to one lacking active squalene synthetase. Given these teachings, the most that can be said of Robinson is that it motivates the development of a gas chromatographic and/or radioassay for squalene synthase activity. For these reasons, Robinson fails to teach or suggest Applicants fluorometric assays for squalene synthase activity.

Serial No: 10/024,130
Filed: 12/17/2001
Page 9 of 11

The secondary references cited in the Office Action fail to correct the deficiencies of Robinson. For instance, Wolf *et al.* is cited for its fluorometric assay for L-glutamic acid decarboxylase (GAD) activity. The assay of Wolf *et al.* is a two-part reaction requiring an enzyme reaction and an indicator reaction. The indicator reaction itself requires two temporally discrete portions: A portion in which NADPH is generated and a separate portion in which the indicator reaction volume is diluted and brought to 1 mL and the fluorescence of the reaction mixture is measured. Applicants' claimed assay is a highthroughput assay that does not require separate enzyme and indicator reactions. Further, Applicants' claimed assay does not require a first temporally discrete portion for the generation of NADPH followed by a second temporally discrete portion in which the reaction is diluted and fluorescence is measured. Rather, Applicants' claimed assay comprises those in which the reaction mixture itself is exposed to UV light and the emitted fluorescence detected. Moreover, Applicants note that the assay of Wolf *et al.* utilizes components distinct from those of Applicants' claimed method. Thus, the assay of Wolf *et al.* fails to teach or suggest any of the methods claimed by Applicants.

Ciosek *et al.* and Nakashima *et al.* also fail to correct the deficiencies discussed above because they disclose only isotopic assays for squalene synthase activity. Given the points of distinction and deficiencies of the presently cited references, one of skill in the art would have neither the motivation for the combination or modification of any of the present references. Further, they would not have a reasonable expectation of successfully developing Applicants' claimed methods. For all of these reasons, Applicants' claimed methods are nonobvious and the rejection should be withdrawn.

With particular respect to claim 16, Applicants respectfully draw the Office's attention to the recitation of identifying a test compound as a candidate herbicide within the claim. As the Office Action notes, the use of squalene synthase inhibitors as herbicides is *not* disclosed in the art. Thus, the art is devoid of any motivation to identify

Serial No: 10/024,130
Filed: 12/17/2001
Page 10 of 11

candidate herbicides by assaying for squalene synthase activity. For this additional reason, the rejection of claim 16 and dependent claims 20-28 should be withdrawn.

Applicants also respectfully draw the Office's attention to claim 29, which recites identifying compounds that selectively inhibit plant squalene synthase. The references cited in the Office Action lack the teaching or motivation to identify compounds that selectively inhibit plant squalene synthase. For this additional reason, the rejection of claim 29 and dependent claims 31-39 should be withdrawn.

CONCLUSION

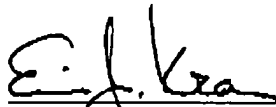
In view of the aforementioned amendments and remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S. C. § 103 are overcome. The Examiner is respectfully requested to withdraw the rejections and allow claims 2-3, 5-16, 20-29 and 31-39. Accordingly, in view of the above remarks, it is submitted that this application is now in condition for allowance. Early notice to this effect is solicited. In any event, the Examiner is respectfully requested to enter the above amendments for purposes of further prosecution. The amendments will not present new issues. If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned

Serial No: 10/024,130
Filed: 12/17/2001
Page 11 of 11

under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 50-0885.

Respectfully submitted,



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